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09/871,809	06/04/2001	Batsheva Kerem	24020X	3895

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1653	6

DATE MAILED: 09/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/871,809	Applicant(s) KEREM, BATSHEVA
	Examiner Chih-Min Kam	Art Unit 1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-8 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-8 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Informalities

The disclosure is objected to because of the following informalities:

1. Nucleotide sequences are cited, for example, at pages 10-12, however, the sequence identifier "SEQ ID NO:" is not given. Appropriate correction is required.

2. Table 1 is cited at page 12, line 25, and page 13, line 15, however, there is no Table 1 shown in the specification. Appropriate correction is required.

3. Table 2 is cited at page 14, lines 5, 6 and 9, however, there is no Table 2 shown in the specification. Appropriate correction is required.

4. At page 12, line 28, the text cites "p3949M", however, the description indicates it is "p3949N". Appropriate correction is required.

5. At page 16, line 3, the text cites "Fig. 7", however, the description indicates it is "Fig. 6". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating individual suffering from cystic fibrosis resulting from an abnormal expression of genes caused by aberrant splicing in cells, comprising administering to the cells or to tissue or organs of the individual comprising the cells, an naturally occurring alternative splicing factor (ASF) by transfected the cells with expression

vector to produce the ASF, whereby the abnormal expression shifts towards normal expression of the gene, does not reasonably provide enablement for a method of treating individual suffering from a disease resulting from an abnormal expression of genes caused by aberrant splicing in cells, comprising administering to the cells or to tissue or organs of the individual comprising the cells, an ASF, whereby the abnormal expression shifts towards normal expression of the gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-8 are directed to a method for treating individual suffering from a disease such as cystic fibrosis resulting from an abnormal expression of genes caused by aberrant splicing in cells, comprising administering to the cells or to tissue or organs of the individual comprising the cells, an ASF, whereby the abnormal expression shifts towards normal expression of the gene. The specification, however, only discloses cursory conclusions without data supporting the findings, which states that the method of invention concerns administering to the cells or to tissue or organs of the individual comprising the cells, an alternative splicing factor (ASF), e.g., [illegible] which is known to modulate alternative splicing, for example, members of the SR protein family including SF2/ASF, the heterogeneous ribonucleoprotein A1 (hnRNP A1), or the agonist of the naturally occurring ASFs, and the administration of the ASFs to the cells or to tissue or organs of the individual comprising the cells, causes a shift in the expression of the gene responsible for genetic disease towards normal expression. There are no indicia that the present application enables the full scope in view of a method for treating a disease resulting from an abnormal expression of genes as discussed in the stated rejection. The present application

provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the absence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding the disease treated, the agonists of naturally occurring ASF administered, and the administration of ASF in various forms, e.g., as a protein product or an expression vector, which are not adequately described or demonstrated in the specification.

(2). The absence of working examples:

There are no working examples indicating the claimed methods in association with the variants except for the examples of several cellular and viral splicing factors that modulate the splicing pattern in epithelial cell lines established from the sample of CF patient (Example 5, pages 14-17).

(3). The state of the prior art and relative skill of those in the art:

Mayeda *et al.* (Mol. Cell. Biology 13, 2993-3001 (1993)) teach the essential splicing factor SF2/ASF and hnRNP A1 modulate alternative splicing *in vitro* of pre-mRNAs. An excess of SF2/ASF prevents inappropriate exon skipping in natural β-tropomyosin pre-mRNA, while an excess of hnRNP A1 does not cause inappropriate exon skipping in natural pre-mRNA;

Nordqvist *et al.* (Mol. Cell. Biology 14, 437-445 (1994)) teach the adenovirus early region 4 proteins E4 open reading frame (E4-ORF3) and E4-ORF6 regulate major late mRNA accumulation by stimulating constitutive splicing. E4-ORF3 facilitates exon inclusion while E4-ORF6 facilitates exon skipping. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on identities of the disease treated and the agonists of ASF administered, and the treating conditions for administering ASF as a protein product or an expression vector, to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass a method for treating a disease resulting from an abnormal expression of genes caused by aberrant splicing in cells, comprising administering to the cells an ASF, whereby the abnormal expression shifts towards normal expression of the gene. As indicated in the prior art (Mayeda *et al.*, Mol. Cell. Biology 13, 2993-3001 (1993)), hnRNP A1 can promote alternative exon skipping, however this effect is not universal and is dependent on the size of the internal alternative exon and on the strength of the polypyrimidine tract in the [illegible]. Therefore, the invention is highly unpredictable regarding the outcome of the treatment without identifying the disease or the agonists of ASF.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method for treating a disease resulting from an abnormal expression of genes caused by aberrant splicing in cells, comprising administering to the cells an ASF, whereby the abnormal expression shifts towards normal expression of the gene. The

specification indicates the effect of overexpression of the cellular hnRNP A1 on the splicing of 3849+10 kb C->T or polyT minigenes, or the effect of overexpression of the viral E4-ORF6 on the splicing of 3849+10 kb C->T minigenes (Examples 2-5; Figs.3-7), where the mutation (3849+10 kb C to T) in the cystic fibrosis transmembrane conductance regulator (CFTR) gene has been linked to CF patients with abnormal epithelial function. However, the specification has not identified any disease other than cystic fibrosis resulting from an abnormal expression of genes caused by aberrant splicing in cells, and there are no working examples indicating the effect of a known ASF in the disease. Furthermore, the specification has not indicated the use of any agonist of naturally occurring ASF, it has not demonstrated the administration of the protein product, ASF to cells is effective in shifting abnormal expression of the gene to normal expression and in the treatment of the disease. There are no working examples indicating the treating conditions such as effective amount of the ASF protein product for a specific disease, and the effect of the ASF in aberrant splicing of the genes and in the treatment of disease. Since the specification fails to provide sufficient guidance on the disease, the agonist of a naturally occurring ASF and the treating conditions for the protein ASF, it is necessary to carry out further experimentation to assess the effects of the ASF in treating the disease due to an abnormal expression of genes caused by aberrant splicing in cells.

(6). Nature of the Invention

The scope of the claims encompass treating a disease resulting from an abnormal expression of genes caused by aberrant splicing in cells, comprising administering to the cells an ASF, whereby the abnormal expression shifts towards normal expression of the gene, but the specification does not identify the disease aside from cystic fibrosis and the agonists

administered, as well as the treating conditions for various diseases using the ASF protein product. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, the working example does not demonstrate the variants, the art is unpredictable regarding the variants, and the guidance and the teaching in the specification are limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of ASF towards various diseases.

7. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-8 are directed to a method for treating individual suffering from a disease (e.g., cystic fibrosis) resulting from an abnormal expression of genes caused by aberrant splicing in cells, comprising administering to the cells or to tissue or organs of the individual comprising the cells, an alternative splicing factor (ASF), whereby the abnormal expression shifts towards normal expression of the gene. The specification indicates that ASF may be administered to the cells by inserting a nucleotide sequence expressing the ASF in an expression vector, and the cells of the individual are transfected with the expression vector to produce ASF, or by attaching the expression vector to targeting moiety, e.g., antibody or a ligand of a specific receptor which can specifically bind to the membranes of the desired cells, and the expression vector being administered systemically, or by administering ASF as the protein product itself (page 5, line 26-page 6, line 25). However, the specification only indicates the effect of overexpression of the cellular hnRNP A1 on the splicing of 3849+10 kb C->T or polyT minigenes, or the effect of

overexpression of the viral E4-ORF6 on the splicing of 3849+10 kb C->T minigenes (Examples 2-5; Figs.3-7), but it has not demonstrated the administration of the protein product, ASF to cells is effective in shifting abnormal expression of the gene to normal expression, and in treating the disease. There are no working examples indicating the treating conditions such as effective amount of the ASF for a specific disease, and the effect of the ASF in aberrant splicing of the genes and in the treatment of disease. Without guidance on the treating conditions of ASF on the disease, one skilled in the art would not know how to use the ASF. The lack of description in treating disease using the ASF as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-8 are indefinite because the claims lack essential steps in the method of treating an individual suffering from a disease resulting from an abnormal expression of genes caused by aberrant splicing. The omitted step is the outcome of the treatment, it is not clear what effect the administration of ASF would produce in the treatment of disease. Claims 2-8 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

9. Claims 1, 2 and 5-9 are indefinite because of the term "a disease" or "an abnormal expression of genes". The term "a disease" or "an abnormal expression of genes" renders the claim indefinite, it is unclear which disease is being treated, and what genes, which are abnormally expressed due to aberrant splicing, are related to the disease. Claims 2 and 5-9 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

10. Claim 5 is indefinite because of the term "SR protein". The term "SR protein" renders the claim indefinite, it is unclear what SR protein represents. A full spelled out name should be indicated.

Conclusion

11. No claims are allowed.

Art of Record

The following references appear to be the closest art to the claimed invention. Mayeda *et al.* (Mol. Cell. Biology 13, 2993-3001 (1993)) teach the essential splicing factor SF2/ASF and hnRNP A1 modulate alternative splicing *in vitro* of pre-mRNAs. An excess of SF2/ASF prevents inappropriate splicing in natural β-tropomyosin pre-mRNA, while an excess of hnRNP A1 does not cause inappropriate exon skipping in natural pre-mRNA; however, the reference does not teach the effect of ASF or hnRNP A1 on genes with aberrant splicing; Highsmith *et al.* (New England J. Med.331, 974-980 (1994)) teach a point mutation (3849+10 kb C to T) in the cystic fibrosis transmembrane conductance regulator (CFTR) gene and a link between the mutation and CF patients with abnormal epithelial function but normal sweat chloride values, however, the reference does not teach the connection between aberrant splicing

and a splicing factor; Nordqvist *et al.* (Mol. Cell. Biology 14, 437-445 (1994)) teach the adenovirus early region 4 proteins E4 open reading frame (E4-ORF3) and E4-ORF6 regulate major late mRNA accumulation by stimulating constitutive splicing. E4-ORF3 facilitates exon inclusion while E4-ORF6 facilitates exon skipping, however, the reference does not teach the effect of E4-ORF3 or E4-ORF6 on genes with aberrant splicing; Chiba-Falek et al. (Genomics 53, 276-283 (1998)) teach the severity of the lung disease associated with CF correlates with the lack of normal CFTR mRNA, and the regulation of alternative splice site selection may be important in developing treatments for cystic fibrosis, and the reference also indicates the 3849+10 kb C to T mutation and the 5T mutation belong to the same class of mutation, however, the reference does not indicate the use of splicing factor for treatment. Therefore, the prior art does not teach using ASF to treat CF and to cause aberrant splicing to shift to normal.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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September 2, 2002